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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/529,053
Filing Date: April 06, 2000
Appellant(s): WILLIAMS ET AL.

Li-Hsien Rin-Laures
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed December 14, 2007 appealing from the Office action mailed July 26, 2007.

(1) **(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

US Patent 5,556,870	Weithmann et al.	September 17, 1996
WO 94/24095	Coghlan et al.	October 27, 1994

McChesney et al. 'An evaluation of leflunomide in the canine renal transplantation model,' Transplantations, 1994, vol. 57, No. 12, pages 1717-1722.

Flamand et al. 'Human herpes virus 6 induces interluekin-1β and tumour necrosis factor alpha, but not interleukin-6, in peripheral blood mononuclear cell cultures,' Journal of virology,' 1991, vol. 65, No. 9. pages 5105-5110.

Hammer 'Advances in antiretroviral therapy and viral load monitoring,' AIDS, 1996, (suppl 3) pages s1-s11.

Colacino 'Mechanism for the anti-hepatitis B virus activity and mitochondral toxicity of fialuridine (FIAU),' Antiviral Research, 1996, Vol. 29, pages 125-139

(9) Grounds of Rejection

Claim Rejections 35 U.S.C. 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claim 46 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly introduced limitation "a pyrimidine compound without antiviral activity" lacks support from the application as originally filed. See, page 20 of the application. "A pyrimidine compound without antiviral activity" is a new concept for the application and constitutes a new matter.

Claim Rejections 35 U.S.C. 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 34, 35, 40, 41 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870) in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11) and Colacino. .

5. Weithmann et al. teach a method of treating disorder in which interleukin 1 beta is involved. The disorders include viral infections, such as HIV or hepatitis, comprising administering leflunomide to the patient. See, particularly, the abstract and the claim. The dosage may range from 3-50 mg daily, but may be higher if required. See, particularly, column 3, lines 7-16.

Weithmann et al. do not teach expressly the employment of addition pyrimidine antiviral agent in the method.

6. However, Hammer teaches that several pyrimidine compounds, including uridine compounds, are known antiviral agents. See, particularly, page s3. Colacino teaches that uridine

compound FIAU is also known to be useful for treatment of hepatitis and herpes infection. See, particularly, pages 125-126.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ a combination of leflunomide compounds with other antiviral agents such as those known pyrimidine compounds Also, it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus , the claimed invention which employ a combination of two known anti-viral agents sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069. Further, combination therapies for viral infection are known to be better than single agent therapy. See, Hammer, page s2, the paragraph of combination therapy.

7. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870) in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11) and Colacino, and in further view of Flamand et al.

Weithmann et al., Hammer, and Colacino as whole do not teach expressly the employment of leflunomide for treatment of herpes infection.

However, Flamand et al. teaches that herpes infection is involved with interleukin 1 beta. See, particularly, the abstract.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the method of Weithmann for treating herpes infections.

A person of ordinary skill in the art would have been motivated to employ the method of Weithmann for treating herpes infections, because herpes infection is known to be involved interleukin 1 beta. Further, the optimization of a result effective parameter, e.g., effective amount for a therapeutical dosage of a known therapeutical agent, is considered within the skill of the artisan. See, In re Boesch and Slaney (CCPA) 204 USPQ 215. It is noted the effective amounts disclosed by Weithmann et al. are well within the effective amounts herein (from 0.1 mg/day to 80 mg/day, see pages 13-19).

8. Claim 34-42 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coghlan et al. (WO 94/24095), in view of McChesney et al. (Transplantation, Vol. 57, no. 12, page 1717-1722), and further in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11), and Colacino.

Coghlan et al. teaches compounds with general structures that encompass leflunomide or its active metabolite, and meet the limitation of general formula as defined in claims 38 and 44, the compounds have similar biological activity of leflunomide or its metabolite. See, particularly, the abstract, page 2, the examples and the claims. The expressly taught compounds includes those meet the leflunomide products (page 18-19 in the specification). Homologue of leflunomide (e.g., 5-methyl-isoxazole-4-carboxylic acid 2,2,2,trifloroethylamide) have been expressly disclosed (page 10, line 35). These compounds are known to be useful for treating or preventing infectious disease caused by pathogenic microorganism, such as hepatitis and cytomegalovirus infection, particularly, HCMV. See, page 3, lines 7-30, page 4, lines 23-32. Note, amide of malononitrile recited in claims 37 and 43 are keto tautomer of the leflunomide

metabolisms as defined in claims 38 and 44, such as A771726, and would have been expected to be the same as those enol tautomers.

Coghlan et al. does not teach expressly the employment leflunomide or its metabolite, or the particular amount herein for treating viral infections. Coghlan et al. (WO 94/24095) do not teach expressly the employment of pyrimidine compound in the method.

9. However, McChesney et al. teaches that both leflunomide and A771726 are known to be effective in preventing viral infection. See, particularly, the abstract at page 1717, and the materials and method at page 1717-1718. Hammer teaches that several pyrimidin compounds, including uridine compounds, are known antiviral agents. See, particularly, page s3. Colacino teaches that uridine compound FIAU is also known to be useful for treatment of hepatitis and herpes infection. See, particularly, pages 125-126.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the compounds taught by Coghlan et al., including both leflunomide and A771726, for treating or prevention viral infections such as hepatitis and CMV, and the others defined herein.

A person of ordinary skill in the art would have been motivated to employ the compounds taught by Coghlan et al., including both leflunomide and A771726, for treating or prevention viral infections such as hepatitis, CMV or other viral infections herein defined, because these compounds are known to be useful for treating or preventing infectious caused by pathogenic microorganisms, and viral infection in particular. Further, both leflunomide and A771726 are known to be similarly useful as the other compounds. Furthermore, the reference

teaches certain compounds that are structural homologs of the instantly claimed leflunomide, i.e., they differ only by a CH_2 group. The instant compounds are structural homologs of the reference compounds when they differ only by a CH_2 group. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compound because such structurally homologous compounds are expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are prima facie obvious, absent a showing of unexpected results. In re Hass, 60 USPQ 544 (CCPA 1944); In re Henze, 85 USPQ 261 (CCPA 1950).

Further, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ a combination of leflunomide compounds, including those disclosed by Coghlan et al, with other antiviral agents such as those known pyrimidine compounds. Also, it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus , the claimed invention which employ a combination of two known anti-viral agents sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069. Further, combination therapies for viral infection are known to be better than single agent therapy. See, Hammer, page s2, the paragraph of combination therapy.

(10) Response to Argument

Appellants' arguments regarding the rejections of claim 46 under 35 U.S.C. 112, first paragraph are not persuasive.

"Without antiviral activity" recited in the claim is not an inherent property of *all* "pyrimidine" encompassed herein. The application gives a very broad definition for "pyrimidine":

As used herein, a "pyrimidine" includes compounds useful either directly or as intermediates in pathways for supplying pyrimidine nucleotides (uridine, cytidine and thymidine). A preferred pyrimidine is uridine. Other suitable pyrimidines include the pyrimidine intermediates orotic acid and orotidine. Other exemplary pyrimidines include cytidine and thymidine, possibly at higher doses. (page 20, lines 12-16 of the specification).

Given their broadest reasonable interpretation in light of the supporting disclosure, (In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023,1027-28 (Fed. Cir. 1997)), the claim would encompass any pyrimidine derivatives, absent evidence to the contrary. The application as originally filed provides no written description as to the antiviral properties of the "pyrimidine." The scope "a pyrimidine compound without antiviral activity" is narrower than that of "a pyrimidine compound." The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

10. The declaration of Dr. Water Atwood assert that the pyrimidine compounds recited in the application would be understood by ordinary artisan as without antiviral activity. However, it is noted the application does not particularly exclude antiviral pyrimidine compounds. The arguments as to the scope of "pyrimidine compounds" are not persuasive. Particularly, "pyrimidine compounds" defined by the application as those compounds having pyrimidine moiety and are " useful either directly or as intermediates in pathways for supplying pyrimidine nucleotides (uridine, cytidine and thymidine). The antiviral agents cited on the record are

deemed to meet such limitation. The examiner agrees that the application does not particularly *require* the "pyrimidine" be antiviral compound. But the application does not exclude any pyrimidine compounds with antiviral activity. The declaration provides no factual data showing the antiviral pyrimidine compounds on the record would not meet the limitation defined herein.

11. As to the rejections under 35 U.S.C. 103, appellant contend that the pyrimidine compounds recited in the references would not meet the limitation of "pyrimidine" herein as the references do not teach the pyrimidine compounds would "enhance serum level of uridine, cytidine or thymidine." The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

12. Further, the application defines the "pyrimidine" as a "pyrimidine" includes compounds useful *either directly or as intermediates in pathways* for supplying pyrimidine nucleotides (uridine, cytidine and thymidine).(emphasis added). All the pyrimidine compounds on the record have a pyrimidine moiety, and would have been reasonably expected to add an intermediate in pathways for supplying pyrimidine nucleotide. The burden in on appellants to produce evidence showing the pyrimidine compounds cited in the references actually do not possessing the property as claimed. In re Fitzgerald, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980). Note, the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). As discussed above, the Atwood declaration fails to provide any factual

evidence showing the antiviral pyrimidine compounds cited in the references would not meet the limitation of "pyrimidine" as defined in the application.

13. Appellants also argue that the claimed invention are patentable over cited prior art because of the unexpected results. The arguments are not persuasive. Regarding the establishment of unexpected results, a few notable principles are well settled. It is applicant's burden to explain any proffered data and establish how any results therein should be taken to be unexpected and significant. See MPEP 716.02 (b). *The claims must be commensurate in the scope with any evidence of unexpected results*. See MPEP 716.02 (d). The claims read on any pyrimidine compounds, while the application merely shows the benefit of uridine (example 2), not all of its derivatives as herein claimed. Therefore, the claims are not commensurate in the scope with the evidence on the record.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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